(ii) substitution of Ile_{96} by a hydrophobic amino acid residue;

(iii) substitution of His_{95} by D-His or by a residue selected from Asp, Glu, Ser, Thr, Phe and Tyr, N-alkyl derivatives thereof and D-forms of the foregoing;

(iv) substitution of Val_{94} by D-Val, or by a residue selected from Ala, His and Phe, and D-forms of the foregoing;

(v) substitution of Ala_{92} by a hydrophobic amino acid residue;

(vi) substitution of Val_{91} by Ala or Gly;

(vii) substitution of Thr_{90} by a residue selected from Asn, Asp, Gln, Glu, Ala, Val and Pro;

(viii) substitution of Val_{89} by a hydrophobic amino acid residue;

(ix) a peptide obtained by elongation of a peptide (i) to (viii) at the N- and/or C-terminal but not including an entire protein;

(x) an amide of the C-terminal of a peptide (i) to (ix); and

(xi) an N-acyl derivative of a peptide (i) to (x).

REMARKS

Claims 1-9, 12 and 13 presently appear in this case. Claims 1-4, 9, 12 and 13 have been rejected, while claims 5-8 have been objected to but indicated to be allowable if rewritten in independent form. The official action of August 21, 2001, has now been carefully studied. Reconsideration and

allowance are hereby respectfully urged.

The present invention relates to a peptide corresponding to positions 89-96 of the human C-reactive protein (CRP) of the formula: Val_{89}-Thr-Val-Ala-Pro-Val-His-Ile_{96} and modifications thereof obtained by substitution, elongation and amidation of the C-terminal or acylation of the N-terminal. The present peptides do not encompass an entire protein. These peptides may be used to inhibit the enzymatic activity of human Leukocyte Elastase (hLE) and/or of human Leukocyte Cathepsin G (hCG) and can be used for the treatment of chronic inflammation conditions such as rheumatoid arthritis, pulmonary emphysema and cystic fibrosis.

The interview between the undersigned attorney and Examiners Hutson and Prouty conducted on November 21, 2001, is hereby gratefully acknowledged. In this interview, it was pointed out that the claimed invention was drawn to a "peptide" and not a full-length protein and, thus, the rejection over Barr should be withdrawn because Barr only discloses full-length proteins. An amendment to claim 1 was suggested in order to clarify that subparagraph (ix) did not read on a full-length protein. The examiners stated that the limitation of the claim to "not a protein" could possibly raise 112, second paragraph, rejections with respect to definiteness. The undersigned showed the examiner several references that supported applicant's position that a peptide and a protein were in fact different and that the difference would have been well-known to those of ordinary skill in the art at the time this invention was made, and thus the language

was not indefinite. The examiners suggested that reconsideration after final rejection would require a new search. Applicant's representative responded that the finality of the present official action was premature. All of the arguments presented in the interview are substantially repeated herein. The examiners indicated that they would carefully consider these arguments at the time that they were submitted in writing.

It is noted that the examiner has considered applicant's arguments of July 27, 2001, to have been persuasive to overcome some of the rejections previously applied, and those rejections or objections not reiterated from previous office actions are withdrawn. Furthermore, the finality of the last office action has been removed.

It is noted that the examiner has made the present rejection a final rejection despite the fact that it includes a new ground of rejection not necessitated by any amendment of applicant. Applicant's response of July 27, 2001, contained no amendment to the claims. The examiner's attention is invited to MPEP §706.07(a) of the new 8th Edition of the Manual of Patent Examining Procedure (MPEP) where it states:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an Information Disclosure Statement ... . Furthermore, a second or any subsequent action on the merits in any application ... will not be made final if it includes a rejection, or newly cited art, other than information

> submitted in an Information Disclosure Statement ... of any claim not amended by applicant ... in spite of the fact that other claims may have been amended to require newly cited art.

Here, claims 1-4, 9, 12 and 13 have been rejected on newly cited prior art. The citation of this prior art could not have been necessitated by amendment of the claims in the previous response as the previous response did not amend the claims. No new IDS has been submitted. Accordingly, the finality of the present official action is premature and should be withdrawn.

Claims 5-8 have been objected to as being dependent on a rejected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

The indication of allowability of claims 5-8 is greatly appreciated. However, for the reasons presented herein, it is believed that the claims from which they depend are now allowable. Accordingly, it should not be necessary at the present time to rewrite these claims in independent form. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-4 and 9 have been rejected under 35 USC 102(b) as being anticipated by Barr. The examiner states that Barr teaches a proteinaceous composition to inhibit naturally occurring serine proteases, which is modified at the active site while maintaining protease inhibition. The examiner states that Barr specifically claims an analog of human α1-antitrypsin wherein the amino acid corresponding to the methionine at position 358 is changed to a valine. The examiner states that

this variant comprises the sequence "... Leu_{353}-Glu-Ala-Ile-Pro-Val-Ser-Ile_{360} ..." which anticipates claims 1-4 and 9. The examiner states that Barr teaches that this variant inhibits human elastase activity. This rejection is respectfully traversed.

The Barr patent relates to the α1-antitrypsin protein that has certain changes in its active site. α1-antitrypsin is another name for α1-protease inhibitor (α1-PI) referred to in the present specification, such as at the top of page 3 and the sequences on page 5 (also see GenBank accession number P01009). The sequence which is relied upon by the examiner is the teaching of Barr which includes the full α1-PI protein with a single amino acid change at Met_{358}. This is the position that corresponds to Val_{94} in the peptide structure of claim 1. It is apparent that the various changes in the core structure of the present protein comprehend the core structure of the α1-PI analog of Barr once the Met has changed in the manner described by Barr. However, claim 1 is not anticipated by Barr because Barr does not comprehend fragments of this protein. Barr only comprehends the entire protein in which the Met_{358} is changed by recombinant technology.

It is apparently the examiner's position that paragraph (ix) of claim 1 reads on an elongation of the peptide to the full extent that it reads on the entire α1-PI (α1-antitrypsin) protein analog of Barr. It is clear from claim 1, however, that the present invention is directed to a peptide and not a protein. Note the preamble which refers to an "isolated peptide". Even

subparagraph (ix) refers to "a peptide obtained by elongation". Thus, even though the peptide may be elongated at the N- and/or C-terminals, this subparagraph requires that that which is obtained after elongation is still a "peptide". The term "peptide" does not comprehend the 394 amino acid protein of antitrypsin (α1-PI) nor does it read on the entire CRP protein, which is over 1,000 amino acids.

The distinction between the term "peptide" and "protein" is well established to those of ordinary skill in the art. Note, for example, Proteins: Structures in Molecular Properties, 2nd Edition by Creighton, W.H. Freeman & Company, New York, 1997, particularly at pages 4 and 5, where it states, in the chapter "Chemical Properties of Polypeptides":

> The following terms are used to describe the various types of polymerized amino acids:
>
> - **Peptide** A short chain of residues with a defined sequence. There is no maximum number of residues in a peptide, but the term is appropriate to a chain if its physical properties are those expected from the sum of its amino acid residues and if there is no fixed 3-dimensional conformation.
>
> - **Polypeptide** A longer chain, usually of defined sequence and length.
>
> ...
>
> - **Protein** Usually reserved for those polypeptides that occur naturally and have a definite 3-dimensional structure under physiological conditions. ...

Dorland's Illustrated Medical Dictionary, 29th Edition, W.B. Sanders Company, Philadelphia, 2000, at page 1348, defines "peptide" as:

> Any member of a class of compounds of low molecular weight that yield two or more amino acids on hydrolysis. They are the constituent parts of proteins and are formed by loss of water from the NH_2 and COOH groups of adjacent amino acids. Peptides are known as di-, tri-, tetra- (etc.) peptides depending on the number of amino acids in the molecule. See also *polypeptide*.

Thus, it can be seen that peptide is a constituent part of a protein, but it is not a protein *per se*.

Organic Chemistry by Fieser & Fieser, 3rd Edition, D.C. Heath & Company, Boston, states at page 447:

> Peptides, arbitrarily defined as protein-like substances of molecular weight less than 10,000, are considerably more stable than proteins and are not subject to denaturation.

This is further confirmation that the known difference between peptides and proteins is that proteins have a fixed three-dimensional structure which is not subject to denaturation, while peptides do not. There is also a molecular weight cut-off of about 10,000.

The following additional definitions have also been found. Basic Principles of Organic Chemistry by Roberts & Caserio, W.A. Benjamin, Inc., New York, 1965, states at 715:

> The distinction between a protein and a peptide is not completely clear. One arbitrary choice is to call proteins only those substances with molecular weights greater than 10,000. The distinction might also be made in terms of differences in physical properties, particularly hydration and conformation. The naturally occurring peptides have relatively short flexible chains and, although hydrated in aqueous solution, are reversibly so; proteins, on the other hand, have very long chains which appear to be coiled and folded in rather

> particular ways, with water molecules helping to fill in the interstices. Under the influence of heat, organic solvents, salts, etc., protein molecules undergo more or less irreversible changes, called **denaturation**, ...

Organic Chemistry by Morrison & Boyd, 4th Edition, Allyn & Bacon, Inc., Boston, 1983, pages 1125-1126 states:

> (By convention, peptides of molecular weight up to 10,000 are known as polypeptides and above that as proteins.)

Introduction to Organic Chemistry by Streitwieser, Jr. & Heathcock, McMillan Publishing Co., Inc., New York, 1976 at page 830 states:

> Peptides, also called polypeptides, are amino acid polymers containing from 2 to about 50 individual units. ...
>
> ...
>
> Peptides are formed by partial hydrolysis of proteins, which are also amino acid polymers of much higher molecular weight (more than 50 amino acid units).

Grant & Hackh's Chemical Dictionary, 5th Edition, McGraw Hill Book Company, New York, 1987, at 431 defines "peptide" as:

> "A compound of 2-10 amino acids ..."

and at 477 defines "protein(s)" as:

> Nitrogenous organic compounds, containing more than about 100 amino acid residues, mol. wt. 8,000-200,000, ...

Ladner et al, U.S. patent 5,837,500 states at column 24, lines 54-58:

> Proteins are polypeptides which, as a result of stabilizing interactions between amino acids that are not in adjacent positions in the chain, have folded into a well-defined conformation.

> This folding is usually essential to their biological activity.

Introduction to Protein Chemistry by Fox & Foster, John Wiley & Sons, Inc., New York, 1957, states at pages 131-132:

> It is first desirable to have a clear idea of the distinction between a peptide and a protein. It is of course easy to differentiate an amino acid and a peptide, but the dividing line between a peptide and protein is highly arbitrary. Unfortunately, the molecular weight and size that permit biological activity are not adequate criteria for such distinctions. The most used arbitrary specification has perhaps been a molecular weight of 10,000. Another property which has been employed is diffusability through cellophane. This criterion has proved a lower limit in size of about 10,000. Similar standards are precipitability by trichloroacetic acid and ammonium sulfate.

Copies of the pages quoted above are attached hereto. All consistently show that those of ordinary skill in the art are aware of the difference between a peptide and a protein. Most define the difference both with respect to conformation (a protein has a fixed conformation which can be denatured, while a peptide does not have such a fixed conformation) as well as molecular weight (usually with a break point of about 10,000).

In order to make explicit in claim 1 that which had been implicit in the term "peptide", paragraph ix has now been amended such that it reads:

> (ix) a peptide obtained by elongation of a peptide (i) to (viii) at the N- and/or C-terminal but not including an entire protein;

Thus, not only are the present claims distinguished from the entire CRP protein, but they are distinguished from the α1-PI protein analogs of Barr. Note McCrady, Patent Office Practice, 4th Edition, 1959, pages 81-2, where it states:

> If a proposed amendment merely expresses the same idea in a different way, or states explicitly an idea which was implicit or inherent in the disclosure of the application as filed, it is proper. The disclosure includes not only what is explicitly shown and described in the application, but also what is fairly to be inferred from the application taken as a whole.

See also MPEP §2163.07. The specification as a whole supports the conclusion that the present invention is directed to peptides, and does not comprehend entire proteins. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 9, 12 and 13 have been rejected under 35 USC 103(a) as being unpatentable over Barr. The examiner states that one of ordinary skill in the art would have been motivated to create a pharmaceutical composition comprising a variant of human α1-antitrypsin wherein the variant comprises the sequence "... Leu_{353}-Glu-Ala-Ile-Pro-Val-Ser-Ile_{360} ..." as taught by Barr, and using such a pharmaceutical composition as an antiinflammatory medication and a means of protecting a host from elastase-related damage to the lungs associated with pulmonary emphysema or acute respiratory distress syndrome. This rejection is respectfully traversed.

As discussed hereinabove, the active principle of the present invention is a peptide and not a protein. Claims

9, 12 and 13 are all ultimately dependent from claim 1 and do not read on methods or compositions which comprehend the entire protein analog of Barr. Accordingly, the rejection of these claims must be withdrawn for the same reasons as discussed above with respect to the anticipation rejection of claim 1.

Regardless of whether or not the finality of the previous official action is withdrawn as requested above, it is urged that the present amendment should be entered and considered at this stage of the prosecution because it really does not add any subject matter to the claim that was not already present. Subparagraph (ix) of claim 1 always required that the product be a peptide and thus it never read on a protein. The proposed amendment merely makes explicit in the claim that which had already been inherently present. Thus, claim 1 never read on full proteins and therefore the present amendment is not that which precipitates any further search, if a further search is necessary as suggested by the examiners at the interview.

It is submitted that all the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
ROGER L. BROWDY
Registration No. 25,618

RLB:al
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
F:\,Y\YEDA\Fridkin1\pto\AmendmentE.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 1 (amended) has been twice-amended as follows:

1 (Twice-Aamended). An isolated peptide capable of inhibiting *in vitro* the enzymatic activity of human Leukocyte Elastase (hLE) and/or of human Cathepsin G (hCG), said peptide being selected from:

(i) a core peptide identical to positions 89-96 of the sequence of human C-reactive protein (CRP) of the formula:

Val_{89}-Thr-Val-Ala-Pro-Val-His-Ile_{96} (of SEQ ID NO:3) or a modification thereof characterized by:

(ii) substitution of Ile_{96} by a hydrophobic amino acid residue;

(iii) substitution of His_{95} by D-His or by a residue selected from Asp, Glu, Ser, Thr, Phe and Tyr, N-alkyl derivatives thereof and D-forms of the foregoing;

(iv) substitution of Val_{94} by D-Val, or by a residue selected from Ala, His and Phe, and D-forms of the foregoing;

(v) substitution of Ala_{92} by a hydrophobic amino acid residue;

(vi) substitution of Val_{91} by Ala or Gly;

(vii) substitution of Thr_{90} by a residue selected from Asn, Asp, Gln, Glu, Ala, Val and Pro;

(viii) substitution of Val_{89} by a hydrophobic amino acid residue;

(ix) a peptide obtained by elongation of a peptide (i) to (viii) at the N- and/or C-terminal but not including ~~the~~ an entire ~~CRP~~protein;

(x) an amide of the C-terminal of a peptide (i) to (ix); and

(xi) an N-acyl derivative of a peptide (i) to (x).